

### ***Remarks***

Reconsideration of this application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-10, 15, 16, 22-29, 31-34 and 36-39, 41 and 44-49 are pending in the application, with claim 1 being the sole independent claim. Claims 1, 5-6, 15-16, 28, 41, 47 and 49 are sought to be amended. Claims 40 and 42-43 are sought to be canceled. No new matter is added by way of these amendments. It is respectfully requested that the amendments be entered and considered.

Support for the amendment of claim 1 can be found, *inter alia*, throughout the specification, *e.g.*, page 9, lines 26-30; page 23, lines 5-9; page 40, lines 20-23. Support for the amendment of claims 5-6 and 49 can be found, *inter alia*, throughout the specification, *e.g.*, page 23, line 17 to page 24, line 22. Support for the amendment of claims 15-16 can be found, *inter alia*, throughout the specification, *e.g.*, page 15, lines 15-26. Support for the amendment of claim 47 can be found, *inter alia*, throughout the specification, *e.g.*, page 37, lines 18-21.

#### ***I. Election/Restriction Requirement***

The Examiner stated that “[n]ewly submitted claims 50-84 are directed to an invention that is independent or distinct from the invention originally claimed”. (Office Action, page 2.)

Applicants have canceled claims 50-84 and filed a divisional application (U.S. Application No. 11/502,546, filed August 11, 2006) with claims substantially similar to canceled claims 50-84.

#### ***II. Claim Objections***

The Examiner objected to claim 28 because of informalities and suggested an amendment to correct the informalities. (Office Action, page 3.)

Applicants thank the Examiner for noting the typographical error. Claim 28 has been amended as suggested by the Examiner. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the objection to claim 28.

**III. Claim Rejections Under 35 U.S.C. § 112, first paragraph**

**A. Claims 47 and 49**

Claims 47 and 49 were "rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement." (Office Action, page 4.) Applicants respectfully disagree.

With regards to claim 47, the Examiner states that "[t]he specification, for example, recites storage of the packaged media at 'temperatures of less than about 20-25° C'". (Office Action, page 5.) Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, claim 47 has been amended to recite "storing the dry powder culture medium at less than about 20°C to 25°C."

With regards to claim 49, the Examiner states "[t]he specification also recites that 'mono- and dibasic phosphate salts are used at concentrations of about 0.1 mM to about 10 mM, from about 0.2 mM to about 9 mM, from about 0.3 mM to about 8.5 mM, from about 0.4 mM to about 8mM, from about 0.5 mM to about 7.5 mM, from about 0.6 mM to about 7 mM, and from about 0.7 mM to about 7 mM'". (Office Action, page 5.) Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, claim 49 has been amended to recite "wherein the at least one buffer salt is a phosphate salt."

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 47 and 49 under 35 U.S.C. § 112, first paragraph.

**B. Claims 1-10, 15-16, 22-29, 31-34, and 36-49**

Claims 1-10, 15-16, 22-29, 31-34, and 36-49 were "rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement." (Office Action, page 5.) Applicants respectfully disagree.

Applicants believe the Examiner's rejection focuses on the size of the genus that results from the combination of (1) different buffer salts with (2) different solvents. For example the Examiner states,

[g]iven the very large genus of *buffer salts and solvents* encompassed by the rejected claims, and given the limited description provided by the prior art and specification . . . the skilled artisan would not have been able to describe the broadly claimed genus of methods for producing eukaryotic dry powder media and said media, such that any buffer salt can be used with any solvent to produced a medium which is automatically pH-adjusting and which "supports the cultivation and/or growth of cells." . . .

(Office Action, page 9, emphasis added.) Applicants respectfully disagree.

To address the Examiner's concerns and advance prosecution, but not in acquiescence to the Examiner's rejection, Applicants have amended claim 1 to recite "reconstitution of said dry powder culture medium with a solvent comprising water".

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-10, 15-16, 22-29, 31-34, and 36-49 under 35 U.S.C. § 112, first paragraph.

**IV. Claim Rejections Under 35 U.S.C. § 112, second paragraph**

Claims 15-16, 22-27 and 44-45 were "rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Office Action, page 10.)

**A. Claims 15 and 16**

Claims 15 and 16 were rejected as being "vague and indefinite in that the metes and bounds of the phrase 'under conditions favoring cultivation of the cell' are unclear". (Office Action, page 10.) Applicants respectfully disagree.

The Examiner asks,

[d]oes Applicant intend to encompass any conditions under which the cells can be maintained or even viably frozen, or does Applicant intend a more narrow set of embodiments in which the conditions allow for, e.g., log phase growth?

(Office Action, page 10.) Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, claims 15 and 16 have been amended to recite "under conditions favoring the growth or differentiation of the eukaryotic cell." Applicants believe that the amendment of claims 15 and 16 addresses the Examiner's concerns.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 15 and 16 under 35 U.S.C. § 112, second paragraph.

**B. Claims 22-27 and 44-45**

The Examiner alleges that claims 22-27 and 44-45 "are vague and indefinite in that the metes and bounds of 'a cell line derived therefrom' are unclear". (Office Action, page 11.) Again, Applicants respectfully disagree.

The scope of the claimed subject matter of claims 22-27 and 44-45 would be readily apparent to one of ordinary skill in the art. A derivative of a parental cell is obtained by modifying the parental cell. Derivatives of a cell line may be obtained using any methods known to those skilled in the art.

Additionally, the United States Patent and Trademark Office (USPTO) uses the term "derivative", without any guidance to the meaning of the term, when referring to various U.S.

Patent Classifications related to cells. As examples, Class 435 subclass 355 is referred to as "blood or lymphatic origin or derivative" (underlining added) and "[s]ubject matter wherein the mouse cell is of blood or lymphatic origin." ("Classification Definitions" as published by the USPTO, June 2005, December 2004 Edition, page 435-97.) Class 435 subclass 357 is referred to as "fibroblast, fibroblast-like cell or derivative (e.g., NIH 3T3, etc.);" (underlining added) and "[s]ubject matter wherein the mouse cell is of fibroblast origin or is most similar to a fibroblast in phenotype." (Classification Definitions, page 435-97.) Class 435 subclass 367 is referred to as "HeLa cell or derivative" (underlining added) and "[s]ubject matter wherein the human cell is of HeLa cell origin." (Classification Definitions, page 435-98.) Therefore, the meaning of a derivative of a cell is well understood and the scope of the claimed subject matter of claims 22-27 and 44-45 would be readily apparent to one of ordinary skill in the art.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 22-27 and 44-45 under 35 U.S.C. § 112, second paragraph.

**V. Claim Rejections Under 35 U.S.C. § 102(b)**

Claims 1-2, 5-8, 10, 15-16, 22-29, 31-34, 36-41 and 44-45 were "rejected under 35 U.S.C. 102(b) as being anticipated by SIGMA catalog 1994" (henceforth SIGMA; Office Action, page 11). Applicants respectfully disagree.

An anticipation rejection under 35 U.S.C. § 102 requires a showing that each limitation of a claim is found in a single reference, practice, or device. (*See In re Donohue*, 766 F.2d 531, 534 (Fed. Cir. 1985).)

SIGMA does not anticipate the present claims because it does not teach an automatically pH-adjusting eukaryotic dry powder culture medium having said desired final pH upon reconstitution and wherein the dry powder culture medium comprises sodium bicarbonate.

Applicants reiterate and incorporate by reference herein the remarks concerning this rejection that were made in the Reply filed in the captioned application and dated March 16, 2006.

The Examiner states,

[t]he SIGMA reference does, in fact, teach a dry powder media comprising sodium bicarbonate. As explained above, both the BGJ<sub>b</sub> medium and the F-12 Coon's Modification medium are taught by the SIGMA reference in variations with and without sodium bicarbonate. . . .

(Office Action, page 14.) Applicants respectfully disagree.

SIGMA may relate to a liquid BGJ<sub>b</sub> medium and a liquid F-12 Coon's Modification medium comprising sodium bicarbonate, but SIGMA does not teach a dry powder medium comprising sodium bicarbonate, as recited in the present claims.

In support of the above, Applicants refer to Product Information documents for SIGMA's BGJ<sub>b</sub> dry powder medium (Product Number F 6636) and the F-12 Coon's Modification dry powder medium (Product Number B 6644), which are provided herewith in Appendix I.

These Product Information documents clearly demonstrate that SIGMA does not teach a dry powder medium comprising sodium bicarbonate. For example, step 4 of the "Preparation Instructions" section states that sodium bicarbonate is added "[t]o the solution". Therefore, it appears that SIGMA does not teach a dry powder culture medium comprising sodium bicarbonate, as recited in the present claims.

Additionally, claim 1 recites "an automatically pH-adjusting eukaryotic dry powder culture medium having said desired final pH upon reconstitution". Steps 4 and 5 of the "Preparation Instructions" demonstrate that neither of the cited dry powder medias in SIGMA are an automatically pH-adjusting eukaryotic dry powder culture medium having the desired final pH upon reconstitution. For example, step 4 involves the addition of sodium bicarbonate to

the reconstituted medium which will typically result in a change of pH relative to the originally reconstituted medium. Step 5 describes adjusting the pH to "0.1-0.3 pH units below the desired pH" (underlining added). Therefore, neither the SIGMA BGJ<sub>b</sub> dry powder culture medium nor the SIGMA F-12 Coon's Modification dry powder culture medium have the desired final pH upon reconstitution, as recited in the present claims.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102(b).

**VI. Claim Rejections Under 35 U.S.C. § 103**

Claims 1-10, 15-16, 22-29, 31-34 and 36-45 were "rejected under 35 U.S.C. 103(a) as being unpatentable over SIGMA (of record) in view of Fike et al (WO 98/36051; of record)." (Office Action, page 16.) Applicants respectfully disagree.

To establish a *prima facie* case of obviousness, the Examiner must, *inter alia*, show that the references upon which she or he relied teach every limitation of the currently claimed invention. (*In re Royka*, 490 F.2d 981, 985 (Fed. Cir. 1974).)

The Examiner states "the construction of the various media set forth in SIGMA involve the determination of a ratio between monobasic and dibasic phosphate salts which give a desired final pH upon reconstitution of the powder." (Office Action, page 16.) Applicants respectfully disagree.

SIGMA does not teach the determination of a ratio between monobasic and dibasic phosphate salts which give a desired final pH upon reconstitution of the powder because as discussed above, the cited dry powder media in SIGMA do not result in a desired pH upon reconstitution of the powder. In addition, the Examiner concedes Fike *et al.* does not disclose

the use of pH-opposing forms of buffer salts in dry powder media.<sup>1</sup> Therefore, Fike *et al.* does not cure the deficiencies of SIGMA. Since SIGMA and Fike *et al.* do not teach every limitation of the currently claimed invention, a *prima facie* case of obviousness has not been established.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 103(a).

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<sup>1</sup> The Examiner has noted that "Fike does not specifically teach using pH-opposing forms of buffer salts to maintain the pH of the medium at a desired level". (Office Action, July 26, 2004, page 6.)




### ***Conclusion***

It is not believed that extensions of time are required beyond those that may otherwise be provided for in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, The United States Patent and Trademark Office is hereby authorized to charge any fee deficiency required to prevent abandonment of the current application or credit any overpayment to Deposit Account 503994.

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete Reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,



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Date: Sept 27, 2006

## Appendix I



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## Product Information

### F-12 COON'S MODIFICATION

With L-Glutamine and 0.863 mg/L Zinc Sulfate

Product Number **F 6636**

#### Product Description

Coon's Modification of Ham's F-12 was developed for culturing hybrid cells that were produced by viral fusion. The modification consists of doubling the amino acids and pyruvate, and including ascorbic acid. The salt concentrations have been altered as well. This formula contains 0.863 mg zinc sulfate per liter, which may render it unsuitable for culturing mouse L-cells.

#### Components

	g/L
Calcium Chloride (anhydrous)	0.1245
Cupric Sulfate $\cdot 5H_2O$	0.000025
Ferrous Sulfate $\cdot 7H_2O$	0.000834
Magnesium Chloride (anhydrous)	0.046659
Magnesium Sulfate (anhydrous)	0.02528
Potassium Chloride	0.305
Potassium Phosphate Monobasic	0.06124
Sodium Chloride	0.517
Sodium Phosphate Dibasic (anhydrous)	0.1324
Zinc Sulfate $\cdot 7H_2O$	0.000863
L-Alanine	0.018
L-Arginine $\cdot HCl$	0.422
L-Asparagine $\cdot H_2O$	0.03
L-Aspartic Acid	0.026
L-Cysteine $\cdot HCl \cdot H_2O$	0.07026
L-Glutamic Acid	0.03
L-Glutamine	0.292
Glycine	0.016
L-Histidine $\cdot HCl \cdot H_2O$	0.042
L-Isoleucine	0.0078
L-Leucine	0.0262
L-Lysine $\cdot HCl$	0.073
L-Methionine	0.009
L-Phenylalanine	0.01
L-Proline	0.07
L-Serine	0.021
L-Threonine	0.0238
L-Tryptophan	0.004
L-Tyrosine $\cdot 2Na \cdot 2H_2O$	0.01586
L-Valine	0.0234
L-Ascorbic Acid $\cdot Na$	0.015

D-Biotin	0.0000073
Choline Chloride	0.01396
Folic Acid	0.00132
myo-Inositol	0.01802
Niacinamide	0.00004
D-Pantothenic Acid (hemicalcium)	0.000238
Pyridoxine $\cdot HCl$	0.00006
Riboflavin	0.00004
Thiamine $\cdot HCl$	0.000337
Vitamin B-12	0.00136
D-Glucose	1.802
Hypoxanthine	0.00404
Linoleic Acid	0.00009
Phenol Red $\cdot Na$	0.00125
Putrescine $\cdot 2HCl$	0.000161
Pyruvic Acid $\cdot Na$	0.22
DL-6,8-Thioctic Acid	0.000206
Thymidine	0.0007

#### Precautions and Disclaimer

##### REAGENT

For In Vitro Diagnostic Use

MSDS Available. Caution - Substance not yet fully tested (EU)

CAUTION: Avoid contact and inhalation.

#### Preparation Instructions

Powdered media are hygroscopic and should be protected from moisture. The entire contents of each package should be used after opening. Preparing a concentrated solution of medium is not recommended as precipitates may form. Supplements can be added prior to filtration or introduced aseptically to sterile medium.

1. Measure out 90% of final required volume of water. Water temperature should be 15-20 °C.
2. While gently stirring the water, add the powdered medium. Stir until dissolved. Do NOT heat.
3. Rinse original package with a small amount of water to remove all traces of powder. Add to solution in step 2.

4. To the solution in step 3, add 2.68 g sodium bicarbonate or 35.7 ml of sodium bicarbonate solution [7.5% w/v] for each liter of final volume of medium being prepared. Stir until dissolved.
5. While stirring, adjust the pH of the medium to 0.1-0.3 pH units below the desired pH since it may rise during filtration. The use of 1N HCl or 1N NaOH is recommended.
6. Add additional water to bring the solution to final volume.
7. Sterilize immediately by filtration using a membrane with a porosity of 0.22 microns.
8. Aseptically dispense medium into sterile container.

#### Storage and Stability

Store the dry powdered medium at 2-8 °C under dry conditions and liquid medium at 2-8 °C in the dark. Deterioration of the powdered medium may be recognized by any or all of the following: [1] color change, [2] granulation/clumping, [3] insolubility. Deterioration of the liquid medium may be recognized by any or all of the following: [1] pH change, [2] precipitate or particulates [3] cloudy appearance [4] color change. The nature of supplements added may affect storage conditions and shelf life of the medium. Product label bears expiration date.

#### Procedure

##### MATERIALS REQUIRED BUT NOT PROVIDED:

Water for tissue culture [W3500]  
Sodium Bicarbonate [S5761] or  
Sodium Bicarbonate Solution, 7.5% [S8761]  
1N Hydrochloric Acid [H9892]  
1N Sodium Hydroxide [S2770]  
Medium additives as required

#### Product Profile

Appearance	Off-white powder
Moisture content	= 2.0%
Solubility	Clear solution at 1x
pH at RT	5.7 ± 0.3
[without sodium bicarbonate]	
pH at RT	7.5 ± 0.3
[with sodium bicarbonate]	
Osmolality	281 mOsm/kg H <sub>2</sub> O ± 5%
[without sodium bicarbonate]	
Osmolality	334 mOsm/kg H <sub>2</sub> O ± 5%
[with sodium bicarbonate]	
Endotoxin	= 1.0 EU/ml at 1x
Amino Acid Analysis	Consistent with formula
by HPLC	
Key Element Analysis	Consistent with formula
by ICAP	

#### Biological Performance Characteristics

Biological performance is assessed using an appropriate cell line(s). Seeding efficiencies, doubling time, and final cell densities are determined. During the testing period cultures are examined microscopically.

#### Reference

1. Coon, H.G. and Weiss, M.C. (1969). A Quantitative Comparison of Formation of Spontaneous and Virus-Produced Viable Hybrids. PNAS, 62, 852-859.

Previous Revision: 1999-01

Revised: 2003-08

**SIGMA®**

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## Product Information

**BGJb MEDIUM**  
**Fitton-Jackson Modification**  
**With L-Glutamine, Without Sodium Bicarbonate**

Product No. **B 6644**  
 Store at 2-8 °C

### Product Description

Medium BGJb was originally developed by Biggers, Gwatkin and Judah in the early 1960's at the Wistar Institute. Subsequent studies resulted in a modification designated BGJb which has been used for supporting cultures of cartilaginous embryonic bone. An additional modification, developed by Sylvia Fitton-Jackson at Strangeways Laboratory in England, is further enriched over the original formula. The additional amino acids and vitamins, and the increased buffering capacity conferred by the phosphates in the Fitton-Jackson modification, create conditions that permit calcification as well as growth of cartilaginous embryonic bone.

BGJb MEDIUM, Product No. B 6644 is one of the cell culture media available from Sigma. The selection of a nutrient medium is strongly influenced by 1) type of cell, 2) type of culture [monolayer, suspension, clonal] and 3) degree of chemical definition necessary. It is important to review the literature for recommendations concerning medium, supplementation and physiological parameters required for a specific cell line.

### Components

	g/L
Magnesium Sulfate	0.09768
Potassium Chloride	0.4
Sodium Acetate	0.05
Sodium Chloride	6.8
Sodium Phosphate Dibasic	0.112
Sodium Phosphate Monobasic	0.02434
L-Alanine	0.25
L-Arginine	0.175
L-Aspartic Acid	0.15
L-Cysteine•HCl•H <sub>2</sub> O	0.1003
L-Glutamine	0.2
Glycine	0.8
L-Histidine	0.15
L-Isoleucine	0.03
L-Leucine	0.05
L-Lysine•HCl	0.24
L-Methionine	0.05
L-Phenylalanine	0.05
L-Proline	0.4
L-Serine	0.2

L-Threonine	0.075
L-Tryptophan	0.04
L-Tyrosine•2Na•2H <sub>2</sub> O	0.05766
DL-Valine	0.065
Ascorbic Acid•Na	0.05
D-Biotin	0.0002
Choline Bitartrate	0.0907
Folic Acid	0.0002
myo-Inositol	0.0002
Nicotinic Acid	0.02
PABA	0.002
D-Pantothenic Acid (hemicalcium)	0.0002
Pyridoxal-5-Phosphate	0.0002
Riboflavin	0.0002
Thiamine•HCl	0.004
α-Tocopherol Phosphate•2Na	0.001
Vitamin B-12	0.00004
Lactic Acid (hemicalcium)	0.555
Glucose	10.0
Phenol Red•Na	0.02

### Precautions and Disclaimer

For R&D use only.  
 Not for drug, household or other uses.

### Preparation Instructions

Powdered media are extremely hygroscopic and should be protected from atmospheric moisture. The entire contents of each package should be used immediately after opening. Preparing a concentrated solution of medium is not recommended as precipitates may form.

Supplements can be added prior to filtration or introduced aseptically to sterile medium. The nature of the supplement may affect storage conditions and shelf life of the medium.

1. Measure out 90% of final required volume of water. Water temperature should be 15-20 °C.
2. While gently stirring the water, add the powdered medium. Stir until dissolved. Do NOT heat.
3. Rinse original package with a small amount of water to remove all traces of powder. Add to solution in step 2.
4. To the solution in step 3, add 3.5 g sodium bicarbonate or 46.6 ml of sodium bicarbonate solution [7.5%w/v] for each liter of final volume of medium being prepared. Stir until dissolved.

5. While stirring, adjust the pH of the medium to 0.1-0.3 pH units below the desired pH since it may rise during filtration. The use of 1N HCl or 1N NaOH is recommended.
6. Add additional water to bring the solution to final volume.
7. Sterilize immediately by filtration using a membrane with a porosity of 0.22 microns.
8. Aseptically dispense medium into sterile container.

#### Product Storage

Store the dry powdered medium at 2-8°C under dry conditions and liquid medium at 2-8°C in the dark. Deterioration of the powdered medium may be recognized by any or all of the following: [1] color change, [2] granulation/clumping, [3] insolubility. Deterioration of the liquid medium may be recognized by any or all of the following: [1] pH change, [2] precipitate or particulate matter throughout the solution, [3] cloudy appearance [4] color change. The nature of supplements added may affect storage conditions and shelf life of the medium. Product label bears expiration date.

#### Materials Required but Not Provided

Water for tissue culture use [W3500]  
Sodium Bicarbonate [S5761] or  
Sodium Bicarbonate Solution, 7.5% [S8761]  
1N Hydrochloric Acid [H9892]  
1N Sodium Hydroxide [S2770]  
Medium additives as required

#### Product Profile

Appearance off-white powder

Moisture content  $\leq 2.0\%$

Solubility clear solution at 1x concentration

pH at RT  $6.2 \pm 0.3$   
[without sodium bicarbonate]

pH at RT  $7.4 \pm 0.3$   
[with sodium bicarbonate]

Osmolality  $325 \text{ mOsm/kg H}_2\text{O} \pm 5\%$   
[without sodium bicarbonate]

Osmolality  $384 \text{ mOsm/kg H}_2\text{O} \pm 5\%$   
[with sodium bicarbonate]

Amino Acid Analysis by HPLC Analysis has confirmed that amino acids are present at concentrations consistent with the formula.

Key Element Analysis by ICAP Analysis has confirmed that key elements are present at concentrations consistent with the formula.

#### Biological Performance Characteristics

Biological performance is assessed using an appropriate cell line(s). Growth studies are carried through 2 subculture generations. Cells are counted and growth is plotted as a logarithmic function of time in culture. Seeding efficiencies, doubling time, and final cell densities are determined. During the testing period cultures are examined microscopically for atypical morphology and evidence of cytotoxicity. Test results are available upon request.

#### References

1. Biggers, J.D., Gwatkin, R.B.L., and Hetner, S., (1961). Growth of Embryonic Avian and Mammalian Tibiae on a Relatively Simple Chemically Defined Medium. Exp. Cell Res., 25:1, 41-58.

Revision date: 2003-11

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